REMARKS

Amendments to the Claims

New claim 30 is added, directed to the direct genotyping of each polymorphic site defining the IL4Rα haplotypes identified in the instant application. Support for this claim is found in the specification at p. 47, line 33 to p. 51, line 16.

Claim Rejections

It is respectfully requested that the rejections to the claims be reconsidered and withdrawn in view of the remarks below.

Claim Rejections under 35 U.S.C. §101

The Office Action rejects claims 26-29 under 35 U.S.C. §101 for lack of utility. These claims are directed to a method for predicting a haplotype pair for the Interleukin 4 Receptor Alpha (IL4Rα) gene of an individual. The Office Action states that the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. The Office Action states that the specification does not contain a clear assertion of utility for the claimed method, and that utility assertions made for the polymorphism and haplotype data disclosed in the specification are neither specific nor substantial with regard to the claimed invention. The Office Action argues that the asserted utilities are not specific to the claimed invention because they could be applied to any set of genetic markers in any gene for the partitioning of the human population and they are not substantial because they are an invitation to do further research in order to determine if the haplotype pairs disclosed herein are actually useful for any particular method.

The Office Action further states that once one has carried out the method of the invention, one has "essentially assigned an arbitrary identifier to the gene of an individual" and that there "is no particular relevance disclosed in the specification for any particular predicted haplotype pair". The Office Action states that since the method is one of estimating a haplotype pair present in an individual rather than a method of "actually determining that any particular haplotype pair is present in the genome of an individual, it is further clear that there is no specific or substantial utility for the arbitrary assignment of a haplotype pair label for an individual".

Reconsideration and withdrawal of this rejection is respectfully requested because utilities for the method are indeed asserted in the specification and the asserted utilities in the specification are specific to this claimed invention, and are substantial and credible, as documented below. Additionally, reconsideration and withdrawal of this rejection is requested because the claimed invention has a well-established utility based on the prior art, also discussed below.

A claimed process is a useful invention under 35 U.S.C. §101 if it produces a product that provides a "specific benefit" existing in "currently available form". *Brenner v. Manson*, 383 U.S. 519, 534, 148 USPQ 689, 695 (1966)). The required degree of this specific benefit is not high; all that is required is that the applicant discloses a practical or real-world benefit that is available from practicing the invention. *See, e.g., Juicy Whip, Inc. v. Orange Bang, Inc.* 51 USPQ2d 1700, 1702 (Fed. Cir. 1999); *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1898-1899 (Fed. Cir. 1996). This practical or real-world benefit need not be explicitly stated in the application but may be obvious to the skilled artisan from what is disclosed in the application. *Cross v. Iizuka*, 224 USPQ 739, 742 (Fed. Cir. 1985); Fed. Reg., Vol. 66, No. 4, 1092, 1098 (U.S. PTO 2001).

The specification asserts that the methods for establishing the IL4Rα haplotype of an individual are useful for, *inter alia*, "predicting individual susceptibility to diseases affected by the expression and function of the IL4Rα protein" (p. 7, lines 11-23). As noted in the specification at p. 3, line 30 to p. 4, line 11, at least three variant amino acid residues in the IL4Rα polypeptide (I75, P503, and R576) were known to be associated with genetic predisposition to one or more allergic inflammatory disorders, e.g. atopy and atopic asthma, or to auto immune disorders, e.g., systemic lupus erythematosus (SLE). Kruse et al. (1999 *Immunology* **96**:365-371, submitted in IDS filed Nov. 9, 2001) reported that presence of both P503 and R576 magnified the effects on signal transduction pathways of IL4Rα. These three IL4Rα variants (I75, P503, and R576) correspond to guanine at PS5, cytosine at PS29 and guanine at PS31 in the IL4Rα genomic structure in the instant application (also see the attached Table A correlating each PS number identified by Applicants with any resultant coding sequence or polypeptide variation). Each of these IL4Rα genomic variants appears in multiple IL4Rα haplotypes disclosed in Table 5. Several of the IL4Rα haplotypes in Table 5 have two or three of these variant alleles previously associated with enhanced disease susceptibility. For example, haplotype 6 (as designated in Table 5) has only one of these three variant alleles that may occur at PS5, PS29 or PS31: G at PS5; haplotype 4 has two: G at PS5 and G at PS31; haplotype 5 has three: G at PS5, C at PS29, and G at PS31, and haplotype 3 has none. Thus, one specific, substantial and credible utility of the method for predicting the IL4Rα haplotype pair present in an individual, which was disclosed within the specification, is the prediction of individual susceptibility to diseases affected by the expression and function of the IL4Rα protein, e.g., atopy, atopic asthma or SLE.

The specification also asserts that the haplotyping methods of the invention are useful in "studying the efficacy of drugs targeting IL4Rα (p.7, lines 11-23). The skilled artisan would have recognized from this assertion and the teachings of the prior art that the results of practicing the claimed method, i.e., the haplotype content determined for an individual, are useful to control for IL4Rα genetic variability in the population when conducting clinical trials of new drugs to treat diseases affected by IL4Rα or one of its molecular complexes or of new drugs directly targeting IL4Rα and molecular complexes including IL4Rα. This specific use of the claimed method does not require that the skilled artisan have any knowledge of how

any IL4Rα haplotype affects activity of the encoded protein or other phenotype. A real-world benefit of using the claimed invention in the clinical trials of drugs to treat diseases affected by IL4Rα or drugs targeting IL4Rα and/or its complexes is to reduce the time and cost of developing such drugs.

Evidence that the skilled artisan would have recognized the utility of the invention by July 13, 2000 is found in a PCT publication, WO 00/33161, which was published June 8, 2000 (Submitted in IDS filed May 8, 2002). This document describes making the treatment and control groups in a clinical trial more genetically homogenous by selecting patients for either group based on their polymorphic profile for one or more genes that may influence response to the drug being studied in the trial. The document explains that selecting patients in this manner reduces the variance in response to the drug that is due to underlying genetic factors, which decreases the size of the confidence interval. A smaller confidence interval allows the skilled artisan to be more confident that any differences in response seen between the treated and control patients is due to the drug, rather than the consequence of genetic differences. Alternatively, genetic matching of the patient and control groups for polymorphisms that may influence drug response allows smaller, and thus less costly, studies to be performed that have the same statistical power as larger studies that do not control for these potentially confounding factors. *See, in WO 00/33161, e.g.*, p. 14, line 1 to p. 15, line 18; p. 23, line3-10; and p. 27, lines 15-29.

It is respectfully asserted that the skilled artisan in the pharmaceutical sciences who was designing a clinical trial of a drug targeting IL4Rα, or one of its complexes, or a drug to treat a disease known to be affected by IL4Rα variants would have immediately recognized the following lessons from the present application combined with WO 00/33161: (1) that variation in the IL4Rα gene may influence response to such a drug based on the effect of known IL4Rα mutants such as the R576E on receptor activity (see the paragraph bridging p.3-p.4 in the specification); (2) that haplotypes spanning the IL4Rα gene are an accurate measurement of this variation; (3) that haplotyping patients for the IL4Rα gene would allow the artisan to selectively assign patients to the treatment and patient groups in a manner to reduce the variance between these groups; and (4) that the immediate, alternative benefits of performing this haplotyping would be (a) increased confidence in the results which would facilitate assessing the desirability of additional trials or (b) smaller, less costly trials with the same confidence level as more traditional size trials. Either of these benefits is consistent with the Federal Circuit's position that inventions in the pharmaceutical arts have sufficient utility under 35 U.S.C. §101 if they make it "inherently faster and easier to combat illnesses and alleviate symptoms." *See Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1899 (1996), *citing Nelson v. Bowler*, 206 USPQ 881, 883 (CCPA 1980).

Applicants also respectfully disagree with the Office Action's allegation that the utilities asserted in the specification are not specific because they could be applied to any set of genetic markers for any gene. The asserted utilities are based on using a *specific* set of haplotypes in the IL4Rα gene to assign a haplotype

pair for the IL4Rα gene to an individual. The assigned haplotype pair may then be used to predict whether the individual is susceptible to *specific* diseases known to be affected by the expression or function of a *specific* protein, IL4Rα, or in studying the efficacy of drugs targeting this *specific* protein, having known *specific* functions, e.g. in the signal transduction pathways in which IL4Rα is known to participate. Other genetic markers in other genes would not "partition the population" in the same way as use of the IL4Rα haplotype pairs assigned by practicing the claimed invention and thus would not achieve the stated objectives of these utilities.

The Office Action also questions the validity of the claimed method of predicting haplotype pairs compared to direct experimental determination of haplotype. At the filing date of the application (and continuing into the present), routine and inexpensive genotyping methods on genomic DNA samples, such as DNA sequencing, typically did not provide phase information (i.e., haplotype information). At the time of filing (as well as currently), phase information for a given individual could be obtained experimentally, but often at considerable cost, by genotyping other family members to establish haplotypes by pedigree or by using one of the available molecular techniques for haplotyping the individual. As a result of the monetary and time costs frequently associated with establishing a haplotype by pedigree or molecular experimental methods, haplotype estimation methods using information for populations to infer haplotypes, such as those of Clark (1990 *Mol Biol Evol.* **7(2)**:111-22, submitted in the attached IDS), Hawley and Kidd (1995 *J. Heredity* **86**:409-411; submitted in the attached IDS) and Stephens JC and Windemuth (WO 01/80156), were known to the skilled practitioner at the time the application was filed to be useful, reliable and cost-effective approaches to determining the haplotype content of an individual in a population. For example, Rieder et al (1999 *Nature Genetics* **22**: 59-62; submitted in the attached IDS), in a study of sequence variation in the human DCP1 gene, note in their methods section (p. 62) that they used the method of Clark (1990) to infer haplotypes and that all inferred haplotypes were confirmed when direct molecular haplotyping was used on a subset of heterozygous sites. Another example demonstrating that the skilled practitioner accepted the validity of statistical methods of inferring haplotypes before the filing date of this application is the work of Ober et al. (2000 *Am. J. Hum. Genet.* **66**:517-526; submitted in the attached IDS), who used a version of the program of Hawley & Kidd, HAPLO, to construct IL4Rα haplotypes in their subjects from the Collaborative Study on the Genetics of Asthma in a study of IL4Rα variation on susceptibility to asthma and atopy. Thus, while the Office Action refers to the prediction method as making "an educated guess at the haplotype", in fact such methods were accepted by the art at the time of filing as valid alternatives to direct determination of the haplotype of an individual by molecular techniques. As discussed in the specification at p. 70, lines 1-10, Applicants used the method described in US provisional application 60/198,340 (which is the priority document for WO 01/80156; submitted in the attached IDS) to infer statistically the haplotypes and haplotype pairs for a total population of 110 individuals, or 220 chromosomes, with duplication of

measurements for 51 individuals between Examples IA and IB. Applicants assert, based on the above cited references, that determining the haplotype pairs for this population using what the Office Action referred to as a first "layer of estimations and assumptions" was in fact viewed by practitioners in the art at the time of filing as a valid and routine approach to determination of haplotypes and haplotype pairs in a population. Similarly based on the above-cited methods, such as Clark (1990), Hawley & Kidd (1995) and WO 01/80156, Applicants further assert that using the haplotype pair information determined for the population, summarized in Table 4, to determine the phasing of the genotypes of yet another individual, as in the claimed method, was also viewed at the time of filing as a valid and useful alternative approach to determining the phasing by direct molecular methods.

For the reasons discussed above, it is respectfully asserted that claims 26-29 meet the utility requirement of 35 U.S.C. §101. Accordingly, Applicants request reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §101

Claim Rejections Under 35 U.S.C. §112, 1st paragraph

Claims 26-29 also stand rejected for lack of enablement. With respect to claims 26-29, one stated ground for rejection under 35 U.S.C. §112, 1st paragraph is that since the invention of these claims did not have a specific, substantial and credible utility, the skilled artisan would not know how to use the claimed invention. It is respectfully requested that this rejection be reconsidered and withdrawn because, as discussed above, practicing the haplotype pair prediction method of claims 26-29 provides a real-world and practical benefit in predicting individual susceptibility to diseases affected by the expression and function of IL4Rα, such as asthma and atopy, and in reducing the time and cost for clinical trials of drugs to treat a disease affected by IL4Rα variants or of drugs targeting IL4Rα.

With respect to claims 26-29, a further ground of rejection under §112, first paragraph, was based on the putative lack of enablement for the method for embodiments in which the identifying step comprises indirectly determining the genotype of one or more IL4Rα polymorphic sites referenced in claim 26. The Office Action argues that neither the specification nor the prior art provides enablement on indirectly determining the genotype of one of the IL4Rα polymorphic sites. The Office Action states that "[i]n particular, the specification does not identify which of the disclosed polymorphisms are in linkage disequilibrium with one another such that the identity of one can reliably be used to predict the identity of another, and further, the specification does not provide any guidance as to any polymorphisms outside of those identified as particular polymorphic sites in the specification that might be in linkage disequilibrium with the recited polymorphic sites."

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

In re Wands, 858 F. 2d 731, 737 (Fed Cir 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F. 2d 731, 737 (quoting Ex parte Jackson, 217 USPQ 804, 807). Based on this test, Applicant believes the Office Action has failed to establish a *prima facie* case of nonenablement of indirect determination of a genotype at one polymorphic site by genotyping a substituting polymorphic site.

As noted in the specification "[T]wo sites are said to be in linkage disequilibrium if the presence of a particular variant at one site enhances the predictability of another variant at the second site (Stephens, JC 1999, *Mol. Diag.* 4: 309-17; submitted in the IDS filed May 9, 2002)." (See p. 49, lines 27-29.) The skilled practitioner would recognize, from perusing Tables 4 and 5 in the specification, which polymorphic sites within the IL4Rα gene are likely to be in high linkage disequilibrium. For example, the alleles present at PS42 and PS45 in any given haplotype track closely together: in general, if an A is present at PS42 an A is present at PS45. In contrast, visual inspection of the alleles at PS44 indicate that they are not highly linked to those at PS45.

The type of experimentation required to quantify the linkage disequilibrium between two such sites identified by the skilled practitioner would have been well-known to him at the time the application was filed. For example, one of the most frequently used measures of linkage disequilibrium, Δ^2, is calculated using the formula described in Devlin, B. and Risch, N. (1995, *Genomics*, 29(2):311-22; submitted in attached IDS). Basically, Δ^2 measures how well an allele X at a first polymorphic site predicts the occurrence of an allele Y at a second polymorphic site on the same chromosome. LD patterns in genomic regions are readily determined empirically in appropriately chosen samples using various techniques known in the art for determining whether any two alleles (at two different polymorphic sites or two haplotypes) are in linkage disequilibrium (Devlin & Risch, *supra*; Weir B.S. 1996 *Genetic Data Analysis II*, Sinauer Associates, Inc. Publishers, Sunderland, MA, pp. 112-133; submitted in attached IDS). The skilled artisan would be able to readily select which method of determining LD will be best suited for a particular sample size and this genomic region. Moreover, the required experimentation to determine a quantitative measure of the linkage disequilibrium between the two sites would not be undue in quantity. Thus, the information disclosed in the specification, in combination with the knowledge of the skilled practitioner based on the prior art, enabled indirect genotyping of a disclosed IL4Rα polymorphic site by genotyping a different IL4Rα polymorphic site disclosed in the specification.

In addition, as noted in the specification at p. 49, lines 29-31, polymorphic sites in linkage disequilibrium with the IL4Rα polymorphic site disclosed in the specification may be located in regions of the gene or in other genomic regions not examined by Applicants. The skilled artisan would have known that these additional polymorphisms in high LD with one or more of the 39 polymorphisms in the disclosed

haplotypes would be in the IL4Rα gene or elsewhere on chromosome 16. Based on information in the prior art on the mean distance along a human chromosome over which linkage disequilibrium exists (Kruglyak L. 1999 *Nature Genetics* **22**:139-44; Collins A. et al. 1999 *Proc. Natl. Acad Sci* **96**:15173-77; Taillon-Miller P et al. 2000 *Nature Genetics* **25**:324-328; all submitted in attached IDS), the skilled artisan would have known that a substituting polymorphic site for a given disclosed IL4Rα polymorphic site would be most likely to be found within about 100 kilobases of that IL4Rα polymorphic site (only 0.003% of the human genome), and that a substituting polymorphic site most likely to have sufficient LD to be useful in association studies was likely to be within 5 kilobases of that disclosed IL4Rα polymorphic site (Dunning et al. 2000 *Am. J. Hum. Genet* **67**:1544-1554; submitted in attached IDS).

The general methodology for screening for polymorphisms within this target region was well-known at the time the application was filed, and a working example of such screening, which targeted exonic regions of the IL4Rα gene is described in Examples 1A and 1B. In addition, a 130 kilobase Genbank sequence, AC004525, including Applicants' reference sequence for the IL4Rα gene, is cited in the specification at p. 3, lines 21-23, and positions of the disclosed polymorphic sites within this publicly available sequence is provided in the specification in Table 3 (p. 67). A method for determining frequencies of polymorphisms, using the novel polymorphisms disclosed in the instant application as an example, is described in the specification at p. 52, lines 30 to p. 53, line 3. As noted above, LD patterns in genomic regions are readily determined empirically in appropriately chosen samples using various techniques known in the art (Devlin & Risch, *supra*; Weir, *supra*). The skilled artisan would be readily able to identify a suitable reference population for this LD measurement. Further, the skilled artisan would be able to readily select which method of determining LD would be best suited for his particular sample size and the genomic region on chromosome 16 extending from the IL4Rα polymorphic site. The skilled artisan would be able to determine the value of LD, e.g. Δ^2, between a substituting polymorphic site and one of the 39 polymorphic sites in the disclosed haplotypes necessary for prediction of a desired accuracy. Thus, the experimentation required to identify additional polymorphic sites in linkage disequilibrium with the polymorphic sites recited in the claim is routine and additionally, the specification provides reasonable guidance on how to perform such experimentation. Thus the amount of experimentation would not be undue. In re Wands, *supra*.

Thus, it is respectfully asserted that the specification in conjunction with the prior art does indeed enable indirect genotyping of disclosed polymorphism and it is requested that this rejection under §112, 1st paragraph be withdrawn.

Supplementary Materials to Aid Examination

Table A below is a revised version of Table 3 for the Examiner's use that provides an additional column with: the nucleotide position for each polymorphic site in SEQ ID NO:1; and also provides two

additional columns providing for each polymorphism that results in polymorphism in the coding sequence the nucleotide position in the coding sequence of the variation and the amino acid position and amino acids associated with each genomic allele. The nucleotide numbers of Figure 1 in the application are offset from those in SEQ ID NO:1 for any given nucleotide position since the figure does not begin numbering at 1 as does the sequence in SEQ ID NO:1. The two additional columns provide the nucleotide position of the polymorphism in SEQ ID NO:2 and the amino acid residues resulting from the reference and variant alleles and position in the polypeptide of SEQ ID NO:3.

All information in Table A may be determined from the application as originally filed.

Conclusion

In view of the foregoing, it is believed that claims 26-30 are in condition for allowance and such favorable action is respectfully requested. Should any questions arise, or if Applicants or Applicants' Agent can facilitate examination of this application, it is respectfully requested that the undersigned Agent be contacted so that any remaining issues can be resolved.

Respectfully submitted,

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